Discrimination of the iNPH group from the AD and control groups using VBM-based ROIs

When using ROIs generated from the results of VBM analyses (Fig. 2a), the relative CSF volumes in the lateral ventricle/Sylvian fissure ROI in the iNPH patients (range, 42.2–81.9%; mean±standard deviation, 60.1±11.6%) were higher than those in the AD patients (23.7–48.6%, 34.2± 7.4%) and controls (14.1–45.0%, 24.1±7.7%; one-way ANOVA, $p<0.001$; post hoc Tukey's test, $p<0.001$; Fig. 2b). Meanwhile, CSF volumes in the high convexity/ midline ROI in the iNPH patients (10.1–26.1%, 16.3± 4.6%) were lower than those in other two groups (AD, 24.3–35.2%, 29.6±3.1%; controls, 18.5–45.1%, 29.6± 6.9%; one-way ANOVA, $p<0.001$; post hoc Tukey's test, $p<0.001$; Fig. 2c). These results corresponded well with the results of the VBM analyses.

In addition, the ratio of the CSF volume in the lateral ventricle/Sylvian fissure ROI to that in the high convexity/ midline ROI in the iNPH patients (2.2–6.2, 3.9±1.2) was remarkably greater than that in the other two groups (AD, 0.7–1.6, 1.2±0.3; control, 0.4–1.6, 0.9±0.3; one-way ANOVA, $p<0.001$; post hoc Tukey's test, $p<0.001$; Fig. 2d). There were no overlaps in this ratio between the iNPH and AD or control groups, and the cutoff level was set to 1.9 (Fig. 2d).

Discussion

By performing VBM analyses using CSF objects extracted from MRI images, we successfully detected significant abnormalities in the CSF space of the iNPH patients. We detected an increase in the CSF space in the lateral ventricle/Sylvian fissure area and a decrease in that in the high convexity/midline area as compared to the corresponding CSF space in AD patients and healthy individuals. The characteristic pattern of reciprocal changes regarding the increase and decrease in the CSF space in

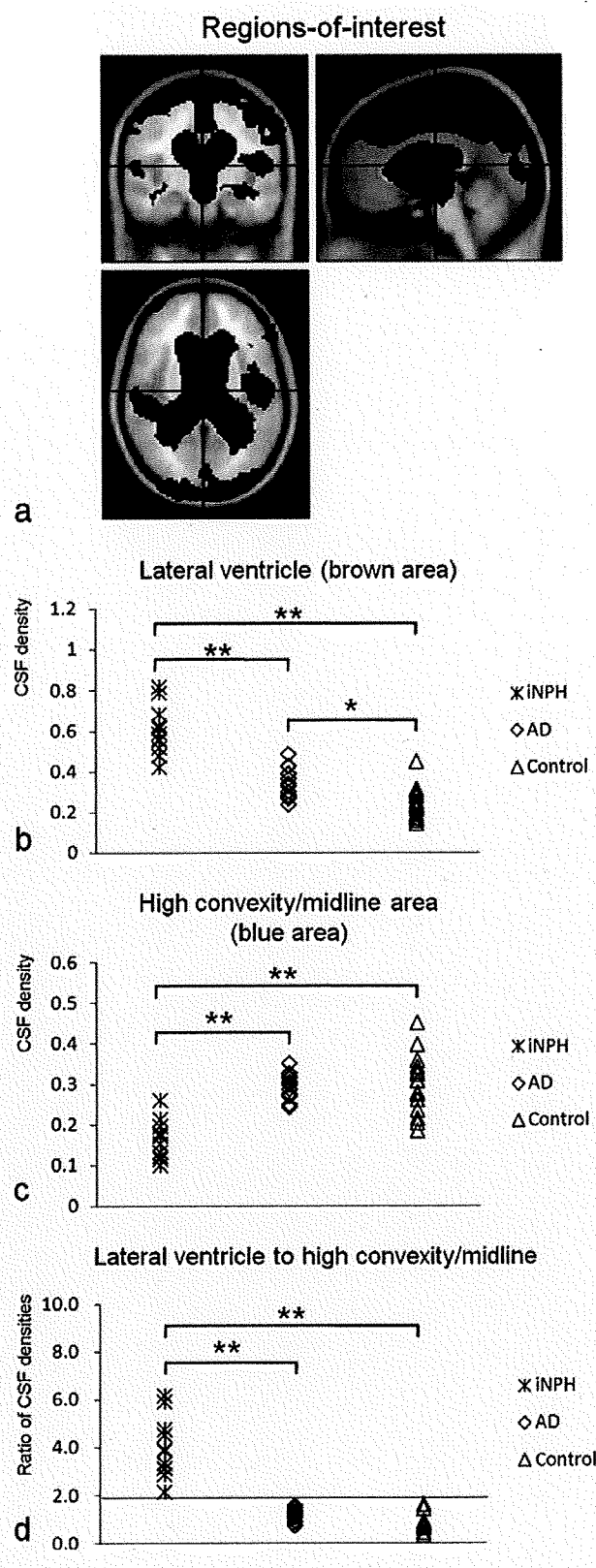

Fig. 2 CSF densities of the two ROIs at the lateral ventricle and high convexity/midline areas, in the iNPH, AD, and control groups. **a** ROIs generated from VBM results (*brown* lateral ventricle area; *blue* high convexity/midline area); **b** CSF density of the ROI at the lateral ventricle area; **c** CSF density of the ROI at the high convexity/midline area; **d** the ratio of the CSF density at the lateral ventricle area to that at the high convexity/midline area. CSF density in the lateral ventricle area was significantly larger and that in the high convexity/midline area was significantly smaller in the iNPH patients than that in the other groups; however, there are substantial overlaps among these groups (**b**, **c**). In contrast, the ratio of the CSF density in the lateral ventricle area to that in the high convexity/midline area is remarkably larger in iNPH patients than that in other groups, without any overlaps; a cutoff line can be placed at a ratio value of 1.9 (**d**). *$p<0.01$; **$p<0.001$

iNPH patients convincingly supports the results of previous studies [3, 4]. Moreover, by using this technique, iNPH can be discriminated from the other conditions when the ratio of the CSF space in the lateral ventricle/Sylvian fissure area to that in the high convexity/midline area is utilized.

In this study, the VBM-based ROIs placed on the lateral ventricle/Sylvian fissure and high convexity/midline areas showed significant differences in the CSF space between iNPH patients and AD patients or healthy controls. However, substantial overlaps were observed among these groups, because ventricular dilatation and narrow high convexity/midline CSF spaces in themselves appear to be relatively nonspecific findings. However, the ratio of the CSF space in the two ROIs could distinguish iNPH patients from the other two groups, without any overlaps. This result suggests that our method can readily detect marked ventricular dilatation paradoxically associated with the substantial narrowing of the high convexity/midline CSF space, which is considered to be a characteristic structural change occurring in iNPH patients, although the mechanisms causing these changes remain unknown.

Accurate diagnosis by noninvasive procedures is one of the important issues in the clinical management of iNPH. Either a CSF tap test with CSF drainage of 30–50 mL or a continuous CSF drainage test is considered effective for determining whether a shunt surgery is indicated [1, 2]; however, noninvasive neuroimaging techniques are needed for guiding these invasive procedures. Marked ventricular dilatation (Evans' index $\geq$0.3), a principal imaging feature in iNPH, is a mandatory but nonspecific finding that can be observed in other hydrocephalic conditions; it may be the result of age-related or abnormal atrophic changes [15]. Several imaging findings such as diffuse white matter lesions, increased CSF flow velocity at the aqueduct, and backflow of the contrast agents or radioisotopes into the lateral ventricle have been reported; however, their diagnostic roles remain controversial [16–18]. Compared with the aforementioned findings, the narrowing of the CSF space in the high convexity/midline areas appears to be more characteristic in iNPH. This finding, however, has always been assessed by visual interpretation, which could be one of the reasons for substantial overlaps between iNPH and other conditions [3, 4]. On the other hand, VBM used to examine a narrowed high convexity/midline CSF space existing along with a dilated lateral ventricle/Sylvian fissure by utilizing the ratio of the CSF space in the two areas is an objective and quantitative method for detecting this characteristic structural change in iNPH. Thus, it may be a potential to become a unique and powerful tool for accurately diagnosing iNPH, although our study did not directly reveal the diagnostic performance of this method or its advantages over other methods.

This study has several limitations. First, we did not perform any comparison between this method and visual interpretations because of the considerable patient selection bias for structural changes. We examined patients with possible iNPH as defined by the guidelines, which signified that all the patients demonstrated marked ventricular dilatation and a narrowed high-convexity CSF space. The AD patients that we examined were diagnosed as probable AD, indicating that imaging findings mimicking iNPH had already been excluded. Hence, a definite advantage of VBM over visual assessment in diagnosing iNPH has not been demonstrated by this study, but it should be determined by prospective studies that enroll patients in whom iNPH is suspected clinically before interpreting imaging findings.

Second, we could not confirm whether this technique can predict the clinical outcome after shunt surgery or whether it can monitor the effectiveness of the procedure, because only two patients in this study underwent the surgery. Furthermore, it remains unknown whether this technique can predict the results of the CSF tap test, because all the iNPH patients included in this study responded positively to the test. Prospective studies with larger sample sizes using the data before and after the procedures are essential for confirming the diagnostic role and clinical significance of VBM in iNPH management.

A technical issue in this study is the accuracy of the automatic segmentation of the CSF objects from the MRI images. We used CSF objects instead of those of the gray matter, which is almost always used in VBM, because the direct assessment of alterations in the CSF space was thus possible as well as because of the difficulty in segmenting gray matter objects in iNPH patients due to remarkable geometric changes and/or white matter lesions. Although several previous studies have used CSF objects [19–21], segmentation of the CSF object can be relatively inaccurate as compared to that of gray or white matter, because there are no probability maps for bone or other non-brain structures in SPM. Although the precision of CSF objects has not been fully validated, our results suggest that the use of CSF objects can contribute to a ready assessment of minute alterations in the CSF spaces in iNPH, and possibly in other neurological disorders such as communicating or non-communicating hydrocephalus with various causes.

Finally, we did not confirm the advantages of the fully automated VBM technique over classical volumetric techniques such as manual tracing and region-growing methods. However, we assume that these classical techniques would not be suitable for measuring alterations in the CSF space in iNPH patients because these techniques may not correctly measure the narrowed CSF space at the high-convexity area due to partial volume effects at the obliterated sulci and cisterns, although these can measure

the volume in the dilated ventricle and Sylvian fissure. In addition, these classical techniques are generally difficult, time-consuming, and can include substantial errors during measurement.

In conclusion, VBM using CSF objects can detect characteristic morphological changes, i.e., the coexistence of a dilated lateral ventricle/Sylvian fissure with a narrowed high convexity/midline CSF space in iNPH patients, by using the ratio of the CSF volume in the two areas. VBM may thus have the potential to detect subtle alterations in the CSF space and accurately discriminate iNPH from other neurological conditions.

Acknowledgments This work was partially supported by a Health and Labour Sciences Research Grant from the Ministry of Health, Labor, and Welfare, Japan (2008-Nanchi-17) and by a Grant-in-Aid for Strategic Medical Science Research Center from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Conflict of interest statement We declare that we have no conflict of interest.

References

1. Relkin N, Marmarou A, Klinge P, Bergsneider M, Black PM (2005) Diagnosing idiopathic normal-pressure hydrocephalus. Neurosurgery 57:S4–S16
2. Ishikawa M, Hashimoto M, Kuwana N, Mori E, Miyake H, Wachi A, Takeuchi T, Kazui H, Koyama H (2008) Guidelines for management of idiopathic normal pressure hydrocephalus. Neurol Med Chir (Tokyo) 48:S1–S23
3. Kitagaki H, Mori E, Ishii K, Yamaji S, Hirono N, Imamura T (1998) CSF spaces in idiopathic normal pressure hydrocephalus: morphology and volumetry. AJNR Am J Neuroradiol 19:1277–1284
4. Sasaki M, Honda S, Yuasa T, Iwamura A, Shibata E, Ohba H (2008) Narrow CSF space at high convexity and high midline areas in idiopathic normal pressure hydrocephalus detected by axial and coronal MRI. Neuroradiology 50:117–122
5. Ashburner J, Friston KJ (2000) Voxel-based morphometry—the methods. Neuroimage 11:805–821
6. Baron JC, Chetelat G, Desgranges B, Perchey G, Landeau B, de la Sayette V, Eustache F (2001) In vivo mapping of gray matter loss with voxel-based morphometry in mild Alzheimer's disease. Neuroimage 14:298–309
7. Karas GB, Burton EJ, Rombouts SA, van Schijndel RA, O'Brien JT, Scheltens P, McKeith IG, Williams D, Ballard C, Barkhof F (2003) A comprehensive study of gray matter loss in patients with Alzheimer's disease using optimized voxel-based morphometry. Neuroimage 18:895–907
8. Rosen HJ, Gorno-Tempini ML, Goldman WP, Perry RJ, Schuff N, Weiner M, Feiwell R, Kramer JH, Miller BL (2002) Patterns of brain atrophy in frontotemporal dementia and semantic dementia. Neurology 58:198–208
9. Josephs KA, Whitwell JL, Dickson DW et al (2008) Voxel-based morphometry in autopsy proven PSP and CBD. Neurobiol Aging 29:280–289
10. Burton EJ, Karas G, Paling SM, Barber R, Williams ED, Ballard CG, McKeith IG, Scheltens P, Barkhof F, O'Brien JT (2002) Patterns of cerebral atrophy in dementia with Lewy bodies using voxel-based morphometry. Neuroimage 17:618–630
11. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34:939–944
12. Ashburner J (2007) A fast diffeomorphic image registration algorithm. Neuroimage 8:95–113
13. Genovese CR, Lazar NA, Nichols T (2002) Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 15:870–878
14. Brett M, Anton J, Valabregue R (2002) Region of interest analysis using an SPM toolbox. 8th International Conference on Functional Mapping of the Human Brain (abstract)
15. Adachi M, Kawanami T, Ohshima F, Kato T (2006) Upper midbrain profile sign and cingulate sulcus sign: MRI findings on sagittal images in idiopathic normal-pressure hydrocephalus, Alzheimer's disease, and progressive supranuclear palsy. Radiat Med 24:568–572
16. Bateman GA, Levi CR, Schofield P, Wang Y, Lovett EC (2005) The pathophysiology of the aqueduct stroke volume in normal pressure hydrocephalus: can co-morbidity with other forms of dementia be excluded? Neuroradiology 47:741–748
17. Tullberg M, Jensen C, Ekholm S, Månsson JE, Fredman P, Wikkelsø C (2001) Normal pressure hydrocephalus: vascular white matter changes on MR images must not exclude patients from shunt surgery. AJNR Am J Neuroradiol 22:1665–1673
18. Vanneste J, Augustijn P, Davies GA, Dirven C, Tan WF (1992) Normal-pressure hydrocephalus. Is cisternography still useful in selecting patients for a shunt? Arch Neurol 49:366–370
19. Della Nave R, Ginestroni A, Tessa C, Cosottini M, Giannelli M, Salvatore E, Sartucci F, De Michele G, Dotti MT, Piacentini S, Mascalchi M (2008) Brain structural damage in spinocerebellar ataxia type 2. A voxel-based morphometry study. Mov Disord 23:899–903
20. Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001) A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 14:21–36
21. Kaasinen V, Maguire RP, Kurki T, Brück A, Rinne JO (2005) Mapping brain structure and personality in late adulthood. Neuroimage 24:315–322

J Neurol
DOI 10.1007/s00415-009-5096-4

LETTER TO THE EDITOR

Depression and psychiatric symptoms preceding onset of dementia in a family with early-onset Alzheimer disease with a novel *PSEN1* mutation

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Received: 9 January 2009 / Revised: 13 February 2009 / Accepted: 27 February 2009

Sirs,

PSEN1 mutations are the most common cause of autosomal dominant early-onset familial Alzheimer disease (EO-FAD) in diverse ethnic groups [1–3]. Cognitive decline is a cardinal clinical feature in patients with *PSEN1* mutations; however, various accompanying clinical manifestations have been reported [4]. We report a family with a novel *PSEN1* mutation who developed depression and psychiatric symptoms preceding the onset of dementia.

The first patient (Patient 1, III-1 in Fig. 1a) has suffered from depression and has undergone antidepressant treatment from the age of 29. She gradually became apathetic at the age of 47. At the age of 48, she developed visual and auditory hallucinations and personality change. She was referred to us for neurological evaluation. Her cognition was impaired as determined using the revised version of the Hasegawa dementia scale (HDS-R) [5] of 11/30. Neurological examination revealed rigidity of the left upper limb and postural instability, suggesting the presence of parkinsonism. Brain MRI showed atrophy of the medial temporal lobe with right predominance. 99mTc-ECD SPECT revealed hypoperfusion in the posterior cingulate gyri as well as in the frontal and parietotemporal cortices with right hemisphere predominance.

The younger sister of Patient 1 (Patient 2, III-2 in Fig. 1a) was diagnosed as having depression when she was in high school. Since then, she has experienced repeated manic and depressive bipolar episodes. Because hallucinations, abnormal cravings, and spatial disorientation were noted at the age of 40, she was admitted to a psychiatric hospital. She was examined by us at the age of 42 and found to exhibit parkinsonian gait, stooped posture, rigidity of limbs, and severe cognitive decline as determined by HDS-R (0/30). Brain MRI showed predominant medial temporal atrophy. 99mTc-ECD SPECT revealed severe hypoperfusion in the posterior cingulated gyri and bilateral parietal area.

On the basis of clinical and imaging findings, we clinically suspected them as having EO-FAD, although they exhibited unusual accompanying symptoms. Their mother, uncles, and grandfather were demented according to an interview with family members (Fig. 1a). A genetic screening of mutations in *APP*, *PSEN1*, *PSEN2*, and *MAPT* was performed after obtaining written, informed consent from the patients and their caregivers. We identified a heterozygous G to C transition in exon 6 of *PSEN1* in the patients, which resulted in a previously undescribed Leu173Phe mutation. This mutation was absent in 110 healthy controls from the same population, as determined by allele-specific PCR methods (Fig. 1b). Codon 173 leucine is located in the third transmembrane domain of *PSEN1* and is highly conserved among species. The *APOE* genotype was 3/4 in both patients.

To examine the pathological characteristics of the *PSEN1* mutation, we established neuroblastoma-derived

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Published online: 12 March 2009

Dementia Japan 23: 14-21, 2009

Early diagnosis of Alzheimer's disease with FDG-PET

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Although there are already many reports about the usefulness of positron emission tomography with FDG (FDG-PET) in diagnosis of Alzheimer disease (AD) and scientific evidence has been established, further improvement in diagnostic accuracy can be achieved by using statistical image analysis, such as SPM and 3D-SSP. FDG-PET is also expected to be able to predict conversion to AD in patients with mild cognitive impairment (MCI), and establishment of the scientific evidence by prospective clinical trial is indispensable. FDG-PET can play an important role in clinical trials for developing new therapeutic drugs for AD.

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